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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/360,199	07/23/99	GAULDIE J	GDI-1

HM12/0606

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EXAMINER	
SCHNIZER, R	
ART UNIT	**PAPER NUMBER**
1632	3

DATE MAILED: 06/06/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

PTO-90C (Rev. 2/95)

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FILE COPY

Office Action Summary	Application No. 09/360,199	Applicant(s) Gauldie
	Examiner Richard Schnizer	Group Art Unit 1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-28 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-28 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 2

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election of Species

Claims 2, 5, and 19 are generic to pluralities of disclosed patentably distinct species.

Claim 2 is generic to patentably distinct species comprising a protein, an antibiotic, an anti-inflammatory, an analgesic, an anti-neoplastic, and a cell. Applicant is required under 35 U.S.C. 121 to elect one of these species, or a single combination of these species, even though this requirement is traversed.

Claim 5 is generic to patentably distinct species comprising a tumor antigen, a cytokine, a growth factor, a marker gene product, an enzyme, a receptor, a receptor agonist, and a structural protein. Applicant is required under 35 U.S.C. 121 to elect one of these species, even though this requirement is traversed.

Claim 19 is generic to patentably distinct species comprising an antigen encoded by a pathogen, a tumor antigen, a cytokine, a growth factor, a receptor, a receptor antagonist, a structural protein, and an antisense nucleic acid. Applicant is required under 35 U.S.C. 121 to elect one of these species, or a single combination of these species, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the

examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Gerard Bencen on 5/25/00 a provisional election was made with traverse to prosecute the invention of claim 2, drawn to a protein; the invention of claim 5, drawn to a tumor antigen; and the invention of claim 19, drawn to an antigen encoded by a pathogen. Affirmation of this election must be made by applicant in replying to this Office action. Non-elected species are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19, 27, 28 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement is considered in view of the *Wands* factors (MPEP 2164.01(a)).

Nature of the invention and scope of the claims. The invention comprises methods of delivering a pharmaceutical composition comprising a nucleic acid to gastrointestinal cells, and methods of disease treatment. The nucleic acid may be an antisense RNA, or it may encode a protein. The nucleic acid may be comprised by a cell. For the purpose of examination, a pharmaceutical composition is considered to be one which provides a therapeutic effect when delivered. Because the purpose of delivering such compositions is to perform therapy, each of claims 1-19, 27, and 28 reads on a method of nucleic acid-mediated therapy. The scope of the claims also encompasses the treatment of any disease in any organism with a gastrointestinal tract.

State of the prior art. At the time the invention was made, successful implementation of nucleic acid-mediated therapy was not routinely obtainable by those skilled in the art. This is reflected by two recently published reviews. Verma et al (1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (1998) states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concludes, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). With respect to antisense-mediated therapies, Crook teaches that although antisense techniques have progressed rapidly, "the technology remains in its infancy", and the utility of the approach is still debatable. See Basic Principles of Antisense Therapeutics, Springer-Verlag, Eds, New York, see pgs. 1-4. Crook also

points out several factors which lend unpredictability to the biological effect of an antisense oligonucleotide (AODN), including the rate of uptake of the AODN, rate of distribution within the target cell, stability within the target cell, local concentration of the oligonucleotide, the concentration and stability of the target mRNA, and the influence of non-antisense effects. In addition, the specification acknowledges that, at the time of the invention, there were no examples of therapeutic benefit from gene transfer to the intestine. This is apparently due to inadequate delivery systems. See page 1, line 25 to page 2, line 18.

Guidance and working examples in the specification. The specification discloses three experiments intended to support enablement of the claimed methods. In one, recombinant adenovirus encoding Pym T antigen was administered to mice intrarectally, lymphocytes were harvested from the mice five days later and shown to lyse specifically cells expressing Pym T antigen *in vitro*. In the second experiment, dendritic cells were transfected *ex vivo* with recombinant adenovirus encoding melanoma gp100 tumor antigen, the cells were then administered subcutaneously to mice, and spleen cells harvested 14 days later were shown to lyse specifically cells expressing gp100 *in vitro*. These two examples demonstrate that lymphocytes can be activated against antigens *in vivo*, but they do not demonstrate that the amount of activation achieved is therapeutically relevant. In addition, the second method does not use the delivery system of the instant invention. The specification also refers to prior art in which colitis was successfully treated in a rat model by intraperitoneal administration of recombinant adenovirus encoding IL-4. See Wan et al (Human Gene Therapy 8: 1355-1363, 7/1997). This

shows that at least a transient therapeutic effect can be acheived in a rat model by administration of nucleic acids. However the delivery method practiced in this example is not the method of the instant invention. In summary, the specification discloses no working example of the instant invention which shows therapeutic effect of the claimed methods *in vivo*. In particular, no guidance or example concerning the use of antisense nucleic acids is presented.

Predictability in the art. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03), and the prior art shows that the art of gene- and antisense-mediated therapy is particularly unpredictable. According to Branch (1998), the ability of antisense to eliminate the function of a single gene has never been proven, and successful delivery of antisense and ribozymes *in vivo* is unpredictable, because the internal structures of the targeted RNAs and their association with cellular proteins can render target sites totally inaccessible in vivo (see abstract; page 49, paragraph bridging columns 1 and 2; and page 49, column two first full paragraph).

In summary, the prior art teaches that success with gene therapy techniques is not routinely obtainable, and the specification discloses that therapeutic benefit had not been obtained through intestinal delivery of gene therapeutics at the time of the invention. Applicant attempts to solve this problem by improving delivery of nucleic acids in the gastrointestinal tract. However no evidence is presented that the methods of the instant invention actually result in any therapeutic effect in the treatment of any disease in any organism. Due to the state of the prior art, the extremely unpredictable nature of the subject matter, and the lack of working examples, one of

skill in the art would have to perform undue experimentation in a order to perform therapy using the methods of the instant invention. With respect to claims 1-19, this rejection can be overcome by deleting the word "pharmacetical" from the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-24, 27, and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-19 are indefinite because the phrase "genitourinary cells" is recited without antecedent basis.

Claim 13 is indefinite because it recites the phrase "nontoxic alcohol". All alcohols are toxic. The claim does not set forth what amount of toxicity is acceptable, or what concentration of alcohol is considered to be nontoxic.

Claims 20-24 are indefinite because they recite the relative term "extended" when describing transgene expression. The metes and bounds of the claims are unclear, because the claim sets forth no basis for comparison. To what does one compare to determine if expression is extended?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 20-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Henning et al (WO 93/19660, published 10/14/93).

Henning teaches a method for delivering biologically active genes to the intestinal epithelium wherein the genes are expressed. See entire document, especially abstract. The nucleic acids may be delivered with a mucolytic agent. See page 11, lines 25-28; and claims 61 and 62 on page 36. The nucleic acid may be comprised within a slow-release capsule. See claim 12, lines 4-8 of page 30. The method may be repeated. See claim 37, lines 1-7 of page 33.

Thus Henning anticipates the claims.

Claim 26 is rejected under 35 U.S.C. 102(b) as being anticipated by Woo et al (US Patent 5,674,703, issued 10/1997).

Woo teaches a suppository comprising a nucleic acid vector encoding a gene. See column 11, lines 20-34, and column 13, lines 8-12.

Thus Woo anticipates the claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached on Mondays and Thursdays between the hours of 6:20 AM and 3:50 PM, and on Tuesdays, Wednesdays and Fridays between the hours of 7:00 AM and 4:30 PM (Eastern time). The examiner is off every other Friday, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached at 703-308-2035. The FAX phone number for art unit 1632 is 703-308-0294.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Richard Schnizer, Ph. D.

BRUCE R. CAMPELL
PRIMARY EXAMINER
GROUP 1800